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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/670,119	NG ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67,69-78,80 and 82-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67,69-78,80 and 82-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 1996* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 9/14/06 has been entered in full. Claims 67, 69, 72-76, 80, 82 and 86 are amended. Claims 68 and 81 are canceled. Claims 1-66 and 79 were previously canceled.

Claims 67, 69-78, 80 and 82-86 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (3/14/06).

The objection to the specification at pg 4 for lack of a descriptive title is *withdrawn* in view of the amended title submitted by Applicants. However, please see the new objection to the specification set forth below.

The objections to claims 67, 72, 82 and 86 at pg 5 are *withdrawn* in view of Applicants' amendments to the claims.

All rejections of claims 68 and 81 are moot in view of Applicants' cancellation of these claims.

The rejection of claims 67, 69-78 and 82-85 at pg 19-21 for containing new matter is *withdrawn in part*. Specifically, the following portion of the rejection is withdrawn: the rejection of the claims for containing a SEQ ID NO: 23 sequence that did not match the SEQ ID NO: 23 sequence contained in the specification originally filed. However, the portion of the new matter rejection based on the lack of support for "peptides comprising at least 16 amino acids" is maintained (see below).

The rejection of claims 69-78 and 82-85 under 35 U.S.C § 112, second paragraph, at pg 20-21 for being indefinite is *withdrawn* in view of Applicants' cancellation of claim 68 and Applicants' amendments to the claims.

The rejection of claim 80 under 35 U.S.C § 112, second paragraph, at pg 20-21 for containing an improper Markush group is *withdrawn* in view of Applicants' amendments to the claim. However, please see the new rejection below of claim 80 under 35 U.S.C § 112, second paragraph necessitated by Applicants' amendments to the claim.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

Claims 67, 69-78, 80 and 82-86 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of treating hypertension in a human comprising administering a peptide consisting of SEQ ID NO: 31, does not reasonably provide enablement for (1) for treating humans with other peptide sequences, including any sequence comprising at least 16 amino acid residues selected from SEQ ID NO: 64-70, with or without side chain modifications or non-natural amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection was set forth at pg 6-15 of the 3/14/06 Office Action, where the Examiner stated:

> "Kinsella et al, 2004 teaches the sequence of each of the seven transmembrane domains of the human alpha-1A adrenergic receptor (see Table 1 on pg 917 of Kinsella et al, 2004. Biochemical and Biophysical Research Communications. 324: 916-921). The alpha-1A adrenergic receptor transmembrane sequences taught by Applicant (pg 23) are derived from the rat receptor (Applicants do not specifically state that these transmembrane domains are from a rat receptor sequence; however, these sequences match the rat receptor sequence disclosed in Figure 2 on page 6368 of Lomasney et al, 1991. Journal of Biological Chemistry, 266(10): 6365-6369). A comparison of the transmembrane region VII of the rat and human sequences reveals that the rat sequence of SEQ ID NO: 29 ('EGVFKVIFWLGYFNSCVNPLIYPCS') is different from the human sequence disclosed by Kinsella ('VFKIVFWLGYLNSCINPIIYPCS')" (pg 10).

As can been seen from the quoted statement, the differences in the transmembrane domain sequences (SEQ ID NO: 23-29) submitted by Applicants (which

Applicants teach are from the α1A adrenergic receptor, also known as the α1A adrenoreceptor) and the sequences of the transmembrane domains of the human α1A receptor taught by Kinsella (2004) led to the conclusion that the specification taught administration of peptides from the rat α1A receptor. However, on further consideration of the specification, the examiner notes that this conclusion is not accurate. Re-examination of the rat sequence taught by Lomasney, 1991, reveals that the transmembrane sequences taught therein also do not entirely match the SEQ ID NO: 23-29 submitted by Applicants. The instant specification at page 50 lists the α1A adrenoreceptor as SwissProt Accession Number P25100. Examination of the record for P25100 reveals that this sequence represents a human α1D adrenoreceptor receptor, which was formerly known as human α1A adrenoreceptor. The relevant art teaches, "The cloned α1D-adrenoreceptor subtype, initially labelled α1A because of the pharmacological similarity of the two subtypes was in fact a new subtype not previously recognized in affinity studies" (pg 198 of Calzada, 2001. Pharmacological Research. 44(3): 195-208). Therefore, the confusion arose due to the fact that two different human adrenergic receptors were at one time known as α1A adrenergic receptor. However, it is now clear that Applicants' working examples with SEQ ID NO: 31 are with a peptide derived from the α1D adrenergic receptor formerly known as α1A adrenergic receptor.

In response to the previous office action, Applicants have amended the claims to replace SEQ ID NO: 23-29 with SEQ ID NO: 64-70. The only claim that is still directed to SEQ ID NO: 31 is claim 80. Comparison of the amino acid sequences of SEQ ID NO: 64-70 with those taught by Kinsella (2004) reveals that SEQ ID NO: 64-70 represent the transmembrane sequences of the human α1A adrenergic receptor. However, the specification does not teach administration of peptides comprising SEQ ID NO: 64-70. As set forth above, the human "α1A adrenergic receptor" taught by Applicants (SwissProt Accession Number P25100) is now known as the α1D adrenergic receptor.

The specification teaches (pg 42-43) that intravenous administration of a peptide consisting of SEQ ID NO: 31 lowered the heart rate and blood pressure of rats administered phenylephrine (a known α1A adrenergic receptor selective agonist). The

peptide of SEQ ID NO: 31 consists of 16 contiguous amino acids derived from transmembrane region VII of the human α1A adrenergic receptor (which is a G-protein coupled receptor or GPCR). The results were similar to those observed with the drug prasozin, a previously characterized α1A adrenergic receptor antagonist. Therefore, administration of the peptide derived from the human α1D adrenoreceptor (former α1A) was able to treat hypertension in rats. In view of this, one of skill in the art would predict that administration of the peptide would also treat hypertension in humans. Therefore, the specification provides enablement for a method of treatment of hypertension in a human comprising administration of SEQ ID NO: 31. However, the specification does not provide enablement for treatment of hypertension in a human with other peptides, including those comprising at least 16 amino acids from SEQ ID NO: 64-70, for the reasons set forth in the 3/14/06 Office Action and reiterated herein.

Applicants' arguments (9/14/06) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons. In the response dated 9/14/06, Applicants argue that according to MPEP 715.07, actual reduction to practice is not required, and that according to MPEP 2164.02, a working example is not needed if one skilled in the art can practice the invention without undue experimentation. Applicants argue that experimentation may be complex if the art typically engages in such experimentation, and may require extended time if the skilled artisan is provided with sufficient guidance. Applicants submit that the instant specification provides sufficient guidance including SEQ ID NO: 31 and methods of screening peptides for antagonist activity. Applicants argue that it is predictable that peptides from all seven transmembrane domains of an α1A adrenergic receptor are able to antagonize said receptor. Applicants point to Tarasova 1999 (cited by the examiner in the previous office action) as teaching peptide antagonists from the second, fourth, sixth and seventh domains of the CXCR4 GPCR, and the instant specification as teaching a peptide antagonist from the fourth, fifth and seventh domains of the D2 dopamine receptor. Applicants argue that in view of the high sequence homology

among GPCRs, it is predictable that peptides from the second, fourth, sixth and seventh transmembrane domains of the α1A adrenergic receptor would be effective antagonists.

Applicants' arguments have been fully considered but are not found persuasive. Applicants argue that there is "high sequence homology among GPCRs", but do not provide any evidence from the relevant art in support of this argument. As set forth in MPEP 2145, "The arguments of counsel cannot take the place of evidence in the record." Instead, the relevant art teaches that while GPCRs have high structural similarity (e.g., seven transmembrane domains), they have little similarity in actual primary amino acid sequences. For example, Wistrand (2006) teaches, "[t]he superfamily is so diverse that many members lack sequence similarity..." (Abstract) and "...GPCRs have high-level features that are more conserved than the primary sequence and make them distinguishable from other proteins" (pg 517; Wistrand et al, 2006. Protein Science. 15: 509-521). Furthermore, the antagonist properties of a particular peptide are hypothesized to result from the interaction with the rest of the receptor sequence, especially the other transmembrane domains (as taught by George et al (2003; cited previously), "We propose that the mechanism of action of the TM-based peptides involves their specific interactions with complementary TM domains/segments within the integral membrane protein)." This suggests that the antagonist properties of a particular peptide are sequence dependent. Tarasova reports that changes of single amino acid residues (either truncations or substitutions) in peptides derived from TM2 altered the antagonist properties of the peptides: "elimination of two C-terminal Asp-residues...decreased antagonist potency more than 10-fold, and substitution of Asp residues with positively charged Lys residues...resulted in a 100-fold decrease in antagonist activity. It is assumed that the charge distribution provides for a proper orientation of the peptides during penetration into the cellular membrane" (pg 34912).

The amended claims still encompass a large number of peptides with different sequences. Claim 67 encompasses a peptide comprising at least sixteen amino acid residues selected from one of SEQ ID NO: 64-70 (which are from the human α1a receptor taught by Kinsella, 2004), each of which is from 22-27 amino acids. In total,

there are over 300 different peptides that consist of at least 16 contiguous amino acids regions that are found with SEQ ID NO: 64-70. Furthermore, claim 67 and dependent claims each encompass innumerable longer sequences comprising each of these different peptides, including the full-length α1A adrenergic receptor. There is no definition of "peptide" in the specification with an upper limit on the length of a "peptide". Claims 74 and 75 broaden the scope of claim 67 to include one or more amino acids in the peptide with side chain modifications (claim 74) or non-natural amino acids (claim 75). Claim 86 broadens the scope of the encompass peptides to those comprising sixteen amino acids from any transmembrane domain from any human α1A receptor.

Each of the sequences of SEQ ID NO: 64-70 are derived from the α1A adrenoreceptor taught by Kinsella (2004) rather than the receptor from which SEQ ID NO: 31 is derived (the α1D adrenoreceptor formerly known as the α1A adrenoreceptor). Applicants have not provided a working example of peptide antagonist of SEQ ID NO: 64-70, or any sequence derived from the α1A adrenoreceptor taught by Kinsella. One of skill in the art would need to screen peptides derived from the α1A adrenoreceptor taught by Kinsella to determine whether or not a peptide can function as *in vitro* antagonist, and then administer any antagonists to rats to determine whether or not any function to treat hypertension. Such experimentation would be undue in view of the large number of peptides encompassed by the claims and the lack of guidance as to predictable changes that can be made to SEQ ID NO: 31 and still produce a peptide that has the same function as SEQ ID NO: 31 (ability to treat hypertension).

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification which of the claimed peptides, other than those consisting of SEQ ID NO: 31, could be used for treatment of hypertension. There are no examples of treatment with a peptide other than SEQ ID NO: 31. Thus the specification fails to teach the skilled artisan how to use the full scope of the claimed methods for treatment without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the claimed methods for the above stated

purpose. Due to the large quantity of experimentation necessary to determine if the full scope of the claimed peptides could be used for treatment of hypertension, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicants have provided is a mere wish or plan and an invitation to experiment.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 67, 69-78, 80 and 82-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 19-21 of the 3/14/06 Office Action.

Applicants' arguments (9/14/06) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons. In the response dated 9/14/06, Applicants request reconsideration and withdrawal of the rejection. Applicants argue that disclosure of the single species of SEQ ID NO: 31 is sufficient to satisfy the written description requirement for the genus of peptides derived from α-1a adrenergic receptor used in the claimed methods. Applicants argue that "[s]ince GPCRs are highly conserved, all GPCRs share substantial sequence similarity, including transmembrane domains defined by a stretch of hydrophobic amino acids."

Applicants' arguments have been fully considered but are not found persuasive. As set forth above, Applicants argue that there is "high sequence homology among GPCRs", but do not provide any evidence from the relevant art in support of this argument. Instead, the relevant art (Wistrand, 2006; cited above) teaches that while GPCRs have high structural similarity (e.g., seven transmembrane domains), but little similarity in actual primary amino acid sequences. Therefore, peptide antagonists

derived from the transmembrane domains from other GPCRs do not provide a description of peptide antagonists derived from the α1A adrenergic receptor. Furthermore, the description of a single peptide antagonist of SEQ ID NO: 31 (derived from the α1A adrenergic receptor of SwissProt Accession Number P25100; now known in the art as α1D adrenergic receptor) does not provide a written description of other peptide antagonists derived from either α1A adrenergic receptor of P25100, or from the α1A adrenergic receptor taught by Kinsella (2004). The claims as amended are directed to methods of treatment using a highly variant genus of peptides derived from the human α1A adrenergic receptor taught by Kinsella (2004). The genus is highly variant because a significant number of structural differences between genus members are permitted. While the specification describes variant peptides, the specification does not describe which variants retain the antagonist activity, other than peptides consisting of SEQ ID NO: 31. Therefore, the instant specification fails to describe the entire genus of peptides that are antagonists that are encompassed by each of the claims.

Therefore, it is maintained for the reasons set forth previously and reiterated herein that only methods comprising administering a peptide consisting of SEQ ID NO: 31, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicants are reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see pg 1115).

Claims 67-78 and 81-86 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for containing new matter. This rejection was set forth at pg 19-21 of the 3/14/06 Office Action.

Applicants' arguments (9/14/06) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response dated 9/14/06, Applicants request reconsideration and withdrawal of the rejection. Applicants' response states at pg 10-11:

> "Applicants point out that the specification (page 8, lines 20-24) states that, "antagonist peptides [comprise] amino acid sequences corresponding to at least four, preferably ten and more preferably from fifteen to twenty consecutive amino acids of an integral protein transmembrane domain." Notably, the antagonist peptides may comprise at least four amino acids of a transmembrane domain. This recitation only includes a lower limitation. The mere fact that fifteen to twenty amino acids are preferable is irrelevant. In Wertheim, the new claim limitation which recited "at least 35%" allowed for species to exceed the 65% limitation originally disclosed in the specification. However, Wertheim is inapplicable to instant claim 67 because the specification adequately described antagonist peptides that comprise at least four amino acids of a transmembrane domain."

Applicants' arguments have been fully considered but are not found persuasive. In *Wertheim*, the specification only taught ranges from 25-60% and the claim which recited at least 35% included embodiments greater than 60%. In the instant case, the specification teaches peptides comprising at least "four, preferably ten and more preferably from fifteen to twenty consecutive amino acids of an integral protein transmembrane domain." There is no upper range placed on the claims; therefore, the fact pattern in *Wertheim* is significantly different than in instant application and the decision is not directly applicable to the instant rejection. However, as set forth previously, there is one example in the specification of a peptide that is 16 amino acids in length, and this does not provide written description for the genus "comprising at least sixteen". Furthermore, the concept of the specific genus does not flow naturally from the disclosure. Therefore, the specification as originally filed lacks support for the genus of molecules encompassed by the amended claims. Applicants teach a range, "comprising...at least four, preferably 10, and more preferably from fifteen to twenty consecutive amino acids". However, a genus may not support a subgenus thought there is a disclosed species with the subgenus. See *In re Smith*, 173 USPQ 679 (CCPA 1972). Furthermore, In *Purdue Pharma L.P. v. Faulding Inc.*, 230F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed. Cir. 2000), the court noted that with respect to In re Ruschig 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that "Ruschig makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention". In order to satisfy the written description requirement,

the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure." In the instant case, the specification disclosed peptides comprising at least fifteen to twenty consecutive amino acids, and there is no guidance directing the skilled artisan to peptides comprising at least sixteen amino acids, despite the single disclosure of a species of sixteen amino acids.

Claims 67, 69-78 and 82-85, in view of the 9/14/06 claim amendments, also each encompass the following new matter: each of the amino acid sequences of SEQ ID NO: 64-70. Applicants' 9/14/06 response at pg 6 states "Applicants also submit a replacement sequence listing containing sequence identifiers for the sequence disclosed in the specification in Table 3 on page 50". However, Table 3 does not contain a reference to any of the specific sequences listed in Table 3. SEQ ID NO: 64-70 are each peptide sequences but each of the sequences referenced in Table 3 are full-length receptor sequences. Applicants do not point to a specific sequence in Table 3. Table 3 lists adrenoreceptor α1A as SwissProt Accession Number P25100. First, the P25100 Accession Number listed in Table 3 refers solely to the full-length adrenoreceptor α1A receptor sequence and does not provide support for any peptide fragments derived from this receptor. Second, the amino acid sequences of SEQ ID NO: 64-70 do not appear to be derived from the sequence of P25100. For example, P25100 contains the sequence "...IVNLAVADLLLSATVLPFSATMEV..." but SEQ ID NO: 64 consists of the sequence "...IVNLAVADLLLSTVLPFSAIFEV".

New objections and/or rejections necessitated by Applicants' amendment

Objections

The amendment filed 9/14/06 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the new sequences presented in the 9/14/06 Sequence Listing including SEQ ID NO: 64; SEQ ID NO: 65; SEQ ID NO: 66; SEQ ID NO: 67; SEQ ID NO: 68; SEQ ID NO: 69; and SEQ ID NO: 70.

Applicants' 9/14/06 response at pg 6 states "Applicants also submit a replacement sequence listing containing sequence identifiers for the sequence disclosed in the specification in Table 3 on page 50". However, Table 3 does not contain a reference to any of the specific sequences listed in Table 3. SEQ ID NO: 64-70 are each peptide sequences but each of the sequences referenced in Table 3 are full-length receptor sequences. Applicants do not point to a specific sequence in Table 3. Table 3 lists adrenoreceptor α1A as SwissProt Accession Number P25100. First, the P25100 SwissProt Accession Number listed in Table 3 refers solely to the full-length adrenoreceptor α1A receptor sequence and does not provide support for any peptide fragments derived from this receptor. Second, the amino acid sequences of SEQ ID NO: 64-70 do not appear to be derived from the sequence of P25100. For example, P25100 contains the sequence "...IVNLAVADLLLSATVLPFSATMEV..." but SEQ ID NO: 64 consists of the sequence "...IVNLAVADLLLSTVLPFSAIFEV".

Applicants are required to cancel the new matter in the reply to this Office action.

Claim Rejections - 35 USC § 112, 2nd paragraph

Claim 80 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 80 as amended recites the limitation "The method according to claim 67 wherein the amino acid sequence of the peptide is VFKVIFWLGYFNSCVN (SEQ ID NO: 31)". There is insufficient antecedent basis for this limitation in the claim. Claim 67 has been amended to recite a Markush group of peptides "comprising at least sixteen (16) contiguous amino acid residues selected from" SEQ ID NO: 64-70. However, none of the amino acid sequences of SEQ ID NO: 64-70 comprise the amino acid sequence of SEQ ID NO: 31. The closest sequence is "VFKIVFWLGYLNSCNINPIIYPCS" (SEQ ID NO: 67) which does not comprise "VFKVIFWLGYFNSCVN" (the differences in the sequences are underlined by the examiner). Therefore, the recitation of SEQ ID NO: 31 in claim 80 lacks antecedent basis.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ruixiang Li

RUIXIANG LI, PH.D.
PRIMARY EXAMINER

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